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Neuropharmacology and analgesia

Tianeptine facilitates spreading depression in well-nourished and early-malnourished adult rats



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ABSTRACT

Nutritional status during development can modify the brain's electrophysiological properties and its response to drugs that reduce the serotonin availability in the synaptic cleft. Here we used cortical spreading depression (CSD) in the rat as a neurophysiological parameter to investigate the interaction between nutritional status and treatment with tianeptine, a serotonin uptake enhancer. From postnatal day 2 to 24, well-nourished and early-malnourished rat pups were s.c. injected with tianeptine (5 or 10 mg/kg; 10 ml/kg) or equivalent volume of saline solution (control group). When the animals were 25–30 days old, CSD was recorded on the brain cortical surface. In the well-nourished rats, but not in the malnourished group, systemic tianeptine dose-dependently increased the CSD propagation velocity, with 10 mg/kg producing a significant ($P < 0.05$) effect. An experiment in adult rats showed that cortical topical application of tianeptine solutions (5 mg/ml, 10 mg/ml, and 20 mg/ml) increased the CSD propagation in both the well-nourished and early-malnourished conditions. In well-nourished animals, 0.5 mg/ml topical tianeptine did not affect CSD propagation, and 2 mg/ml produced a small, but significant CSD acceleration. Our results indicate a facilitating action of tianeptine on CSD propagation, probably via tianeptine's pharmacological action on the serotonin system. These findings support previous data suggesting an antagonistic role of the serotonergic system on CSD.

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1. Introduction

Nutritional status during development is an exogenous factor that can influence the mammalian brain (Borba et al., 2000; Morgane et al., 1993; Picanço-Diniz et al., 1998). It has been reported that nutritional status can modulate levels of several neurotransmitters in the brain, either in early stages of life or in adulthood, and there is some evidence that malnutrition can interfere with serotonin activities in the brain (Manhães-de-Castro et al., 2001; Manjarrez et al., 1998).

Serotonergic neurons are among the first to develop in the mammalian brain, and can act as a trophic factor for the development of other neurons (Azmitia and Whitaker-Azmitia, 1995; Lauder et al., 1981). Serotonin reportedly has an antagonistic action on epileptic seizures and migraine, two neurological

disorders associated with changes in brain excitability (Gold et al., 1998; Lu and Gean, 1998; Salgado-Commissariat and Alkadhi, 1997). Moreover, the serotonergic system has been shown to counteract cortical spreading depression (CSD), a brain electrophysiological phenomenon that is also related to neuronal excitability (Amancio-dos-Santos et al., 2006; Guedes et al., 2002). This relationship is analyzed in the present work.

CSD is a self-propagating wave of depolarization associated with depression of spontaneous and evoked neuronal bioelectrical activity, which lasts for several minutes before completely recovering (Gorji, 2001). CSD can be induced with different stimuli (Burés et al., 1974; Leão, 1944; Leão and Morrison, 1945) and it has been postulated that its mechanisms are related to those of the relevant human neurological diseases epilepsy, migraine, and brain ischemia (Leão, 1944; Lehmenkühler et al., 1993; Takano et al., 1996). Under normal conditions, the cortical tissue presents a certain degree of resistance to CSD propagation; experimental manipulations can increase or decrease such resistance, resulting in, respectively, lower or higher CSD velocities of propagation (Guedes and Do-Carmo, 1980; Rocha-de-Melo et al., 2006). Therefore, the susceptibility of the brain to CSD can be

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adequately estimated from the CSD propagation velocity along the cerebral cortex. Studying the pharmacological experimental conditions that facilitate or impair the brain's ability to produce and propagate CSD can advance our understanding of electrophysiological brain phenomena and related diseases (Costa-Cruz et al., 2006; Guedes and Cavalheiro, 1997). It has been established that serotonin-enhancing drugs decrease CSD propagation, suggesting an antagonistic action of serotonin on CSD (Cabral-Filho et al., 1995; Guedes et al., 2002; Amancio-dos-Santos et al., 2006). However, no information is available regarding the CSD effects of drugs like tianeptine that diminish brain serotonin availability.

The present study of young and adult rat brains subjected to systemic and topical tianeptine application addresses three questions: (1) how does systemic administration of tianeptine during brain development subsequently affect CSD propagation? (2) after brain development, does topical application of tianeptine in the adult rat affect CSD? and (3) how are the systemic and topical effects of tianeptine on CSD influenced by the previous nutritional condition?

2. Materials and methods

2.1. Animals and suckling conditions

Newborn Wistar rats ($n=104$) were raised under one of the following two nutritional conditions during the suckling period: (a) well-nourished ($n=57$), i.e., suckled by dams fed a standard lab chow diet (Purina do Brasil Ltd., Paulinia, São Paulo, Brazil) with 23% protein; or (b) early-malnourished ($n=47$), i.e., suckled by dams fed a deficient diet containing 8% protein. The animals were handled in accordance with the standards of the Ethics Committee for Animal Research, of the Universidade Federal de Pernambuco, Brazil, which comply with the "Principles of Laboratory Animal Care" (NIH; Bethesda, USA).

2.2. Systemic tianeptine treatment

Well-nourished and malnourished animals were treated subcutaneously with 5 or 10 mg/kg/day tianeptine ($n=9$ and 7, respectively, for the well-nourished condition, and $n=10$ and 9 for the malnourished condition) or an equivalent volume (10 ml/kg) of saline ($n=7$ and 8, respectively, for the well-nourished and malnourished conditions). Injections were given at 7 a.m. daily throughout the suckling period (postnatal days 2–24). Each rat pup was weighed daily during the suckling period and on the day of the CSD recording (between postnatal day 25 and 30).

2.3. Cortical topical tianeptine treatment

Tianeptine solutions containing 5, 10, or 20 mg/ml were topically applied in three groups each of well-nourished and malnourished adult rats (90–150 days old; $n=9$, 8, and 7 for the well-nourished condition, and $n=6$, 8, and 6 for the malnourished condition). This topical application was performed on two circular portions (3- to 4-mm diameter) of the cortical surface (over the intact dura-mater) where the recording electrodes were placed. After 1–2 h of baseline CSD recording, tianeptine was applied during the last 10 min of the 20-min interval between two consecutive CSD-eliciting KCl-stimulations (see below). At the end of the 10-min topical application, the treated region was dried with a piece of cotton immediately before the next CSD episode was elicited. After the tianeptine-effect had been documented, at least three subsequent CSD episodes were stimulated without any drug application in order to document the recovery of CSD-features. CSD propagation velocities recorded after topical application of tianeptine were compared to mean values obtained in the same animals during the baseline period.

In the well-nourished condition, topical application of 0.5 mg/ml and 2 mg/ml of tianeptine were also tested ($n=5$ for each concentration).

2.4. CSD recording

On the day of the CSD recording, the rats were anesthetized i.p. with a mixture of 1000 mg/kg urethane plus 40 mg/kg chloralose, and three trephine holes were drilled on the right side of the skull. These holes were aligned in the frontal–occipital direction and were parallel to the midline. CSD was elicited at 20 min intervals by 1-min topical application of 2% KCl solution to the anterior hole (2 mm in diameter) drilled at the frontal region. The two other holes (3–4 mm in diameter) on the parieto-occipital region served as recording places. Both the cortical spontaneous electrical activity (electrocorticogram; ECoG) and the slow potential change accompanying CSD were continuously recorded for 4 h, using two Ag–AgCl agar-Ringer electrodes (one in each hole) against a common reference electrode of the same type placed on the nasal bones (see inset of Figs. 2 and 4). The CSD velocity of propagation was calculated from the time required for a CSD wave to pass the distance between the two cortical recording points. During the recording period, rectal temperature was maintained at 37 ± 1 °C by means of a heating blanket. At the end of the session, the animal was killed with an overdose of anesthetic.

2.5. Statistics

Body weights, as well as CSD velocities, were compared using ANOVA followed by post-hoc (Tukey–Kramer) test, when indicated. The paired *t*-test was employed to analyze the effects of topical tianeptine application by comparing, in the same animal, CSD-features before and after the treatment. Differences were considered significant when $P < 0.05$.

3. Results

3.1. Body weights

As shown in Fig. 1, early-malnourished rats displayed lower body weights than the well-nourished animals, both at 25–35 days and 90–120 days of life. In the young group, body weights of the rats treated systemically with tianeptine did not differ from those of saline-treated rats with the same nutritional status (data not shown).

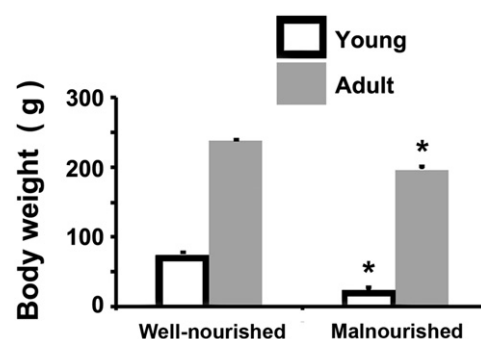


Fig. 1. Body weights of young and adult rats that were well nourished and malnourished during the lactation period. Data are presented as mean \pm S.E.M. Asterisks in the malnourished groups indicate significant weight reduction compared with the respective well-nourished groups. (ANOVA plus Tukey-test; $P < 0.05$). Young well-nourished, $n=7$; Adult well-nourished, $n=9$; Young malnourished, $n=8$; Adult malnourished, $n=10$.

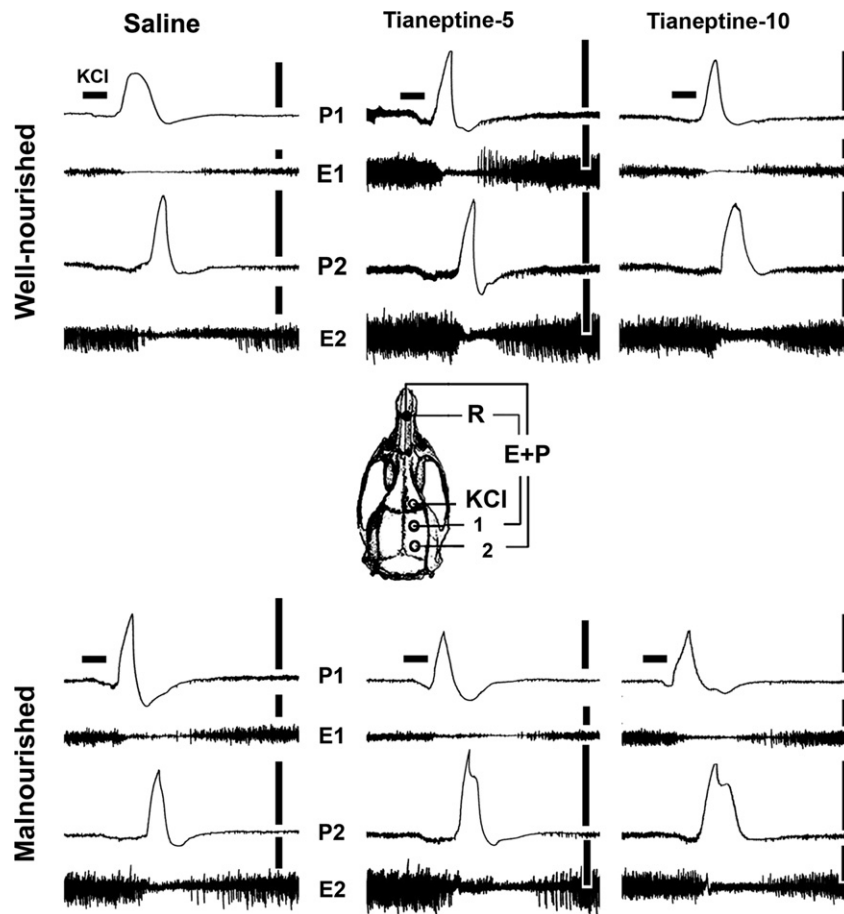


Fig. 2. Electrocorticogram (E) and slow potential change (P) recordings in well-nourished and malnourished young rats (25–30 days old) that were treated during the lactation period with s.c. injections of tianeptine (5 mg/kg or 10 mg/kg) or saline solution (10 ml/kg). The center inset shows recording positions 1 and 2, as well as the position of the common reference electrode (R). CSD was elicited by 2% KCl applied for 1 min to the frontal cortex at the time indicated by the horizontal bars (P1-traces). The vertical bars correspond to 10 mV in P and 0.5 mV in E (negative upward).

3.2. Cortical CSD propagation

3.2.1. Systemic tianeptine treatment

Fig. 2 illustrates ECoG and DC-recordings in the parietal cortex of three well-nourished and three malnourished rats that were treated systemically with saline or tianeptine at doses of 5 or 10 mg/kg. Stimulation with KCl for 1 min consistently elicited CSD, which propagated and was recorded by the two electrodes at the parietal surface of the same hemisphere (see stimulation and recording places at the inset of Fig. 2). After a few min of recording CSD, we observed the gradual return of the ECoG and the slow potential changes back to the pre-CSD levels.

As a rule, we recorded 10 to 12 CSD episodes (elicited at 20 min intervals), and we calculated the mean CSD velocity of propagation for each animal. Fig. 3 shows these mean values for the saline, tianeptine-5, and tianeptine-10 groups. In the well-nourished animals, early systemic tianeptine treatment resulted in higher CSD velocities compared to those of the corresponding saline-treated groups; the CSD velocity increase was statistically significant when the highest dose was administered (group tianeptine-10; left panel of Fig. 3), suggesting that the systemic effect of tianeptine on CSD was dose-dependent (Fig. 3, left panel). The mean velocities (\pm standard deviation) for the well-nourished groups treated with saline, and 5 and 10 mg/kg tianeptine were, respectively, 3.86 ± 0.25 , 3.96 ± 0.11 , and 4.61 ± 0.34 mm/min.

When compared to the well-nourished animals, malnourished rats presented higher CSD velocities. In the malnourished rats, systemic tianeptine treatment did not result in significant CSD

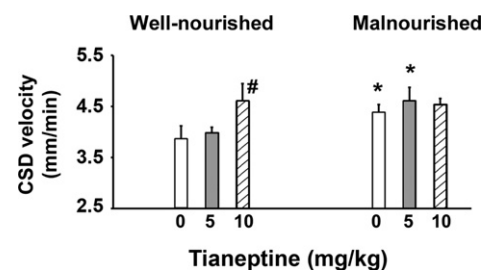


Fig. 3. CSD velocities in well-nourished and malnourished young rats (25–30 days old) that were treated during the lactation period with s.c. injections of tianeptine (5 mg/kg or 10 mg/kg) or with a corresponding volume of saline solution (10 ml/kg). Values are expressed as mean \pm S.E.M. # denotes that the CSD velocity in the well-nourished tianeptine-10 group is significantly higher ($P < 0.05$) than in the respective saline group. Asterisks indicate malnourished groups with higher CSD-velocities compared with the corresponding well-nourished groups ($P < 0.05$; ANOVA plus Tukey test). The saline group is represented by the white bar.

enhancement compared to in the saline group (right panel of Fig. 3). The mean velocities (\pm standard deviation) for the malnourished groups treated systemically with saline, and 5 and 10 mg/kg tianeptine were, respectively, 4.38 ± 0.16 , 4.61 ± 0.27 , and 4.53 ± 0.13 mm/min.

3.2.2. Topical cortical treatment with tianeptine

Fig. 4 illustrates the effect of topical treatment with 10 mg/ml tianeptine solution on CSD propagation. In both well-nourished

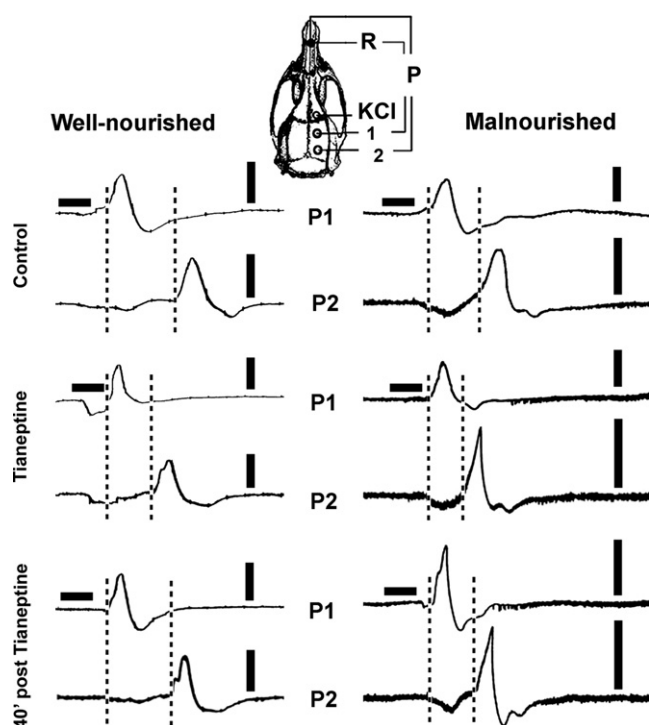


Fig. 4. Slow potential change (P) recordings in well-nourished and early-malnourished adult rats (90–150 days old) showing the effects of topical applications of tianeptine solution (10 mg/ml) on CSD. The upper-central inset shows recording positions 1 and 2, as well as the position of the common reference electrode (R). CSD was elicited by 2% KCl applied for 1 min to the frontal cortex at the time indicated by the horizontal bars (P1-traces). The vertical bars correspond to 10 mV (negative upward). In every animal, **Control**: a baseline CSD recording, i.e., before tianeptine topical treatment; **Tianeptine**: represents the topical drug treatment period. The tianeptine recordings show a decrease in the latency of a CSD wave crossing the distance between the two recording points. **40' post-Tianeptine**: the recovery from the topical drug effect, which was reached 40 min after tianeptine removal.

and malnourished rats, a drop of tianeptine solution was applied for 10 min over the intact dura mater at both trephine holes used for the electrophysiological recordings. This application decreased the latency (i.e., enhanced the velocity) of a CSD wave crossing the distance between the two recording points. After tianeptine removal, the CSD propagation velocity returned to the pretreatment levels (see the time between the dashed lines in Fig. 4).

Fig. 5 presents the increase of CSD velocities in well-nourished and malnourished rats after topical application of the tianeptine solutions. In the well-nourished animals, treatment with 0.5 mg/ml tianeptine did not change the CSD velocity, as compared to the control values. Application of the more concentrated solutions (2, 5, 10, and 20 mg/ml tianeptine) produced significant, dose-dependent increases in CSD propagation velocity. The maximal percent increases of CSD velocity (mean \pm standard deviation) were $11.8 \pm 2.7\%$, $18.8 \pm 5.8\%$, $19.9 \pm 7.7\%$, and $20.5 \pm 8.6\%$, respectively. In the malnourished groups these significant percent increases were, respectively, $19.7 \pm 11.1\%$, $16.0 \pm 6.9\%$, and $30.1 \pm 11.9\%$. The maximal CSD velocity increases were attained between 10–110 min after tianeptine application, and the recovery of these tianeptine effects took 20–80 min after the maximal increase.

4. Discussion

Here we demonstrated for the first time that systemic administration of the serotonin reuptake enhancer tianeptine during brain development had an accelerating effect on CSD propagation.

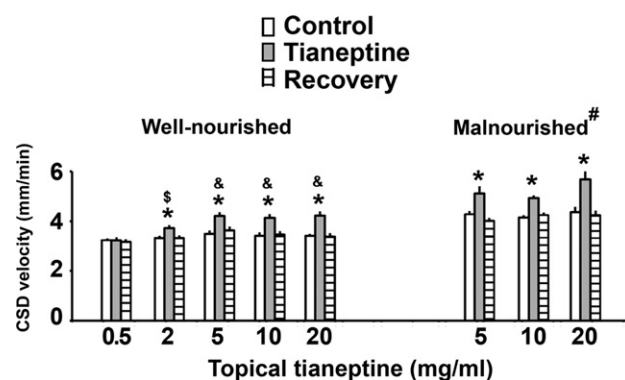


Fig. 5. Enhancements of CSD-velocity in adult rats who were well nourished and malnourished in the lactation period, after topical cortical application of tianeptine solutions during the 10 min immediately preceding CSD elicitation with KCl. Tianeptine was topically applied to a circular area (3- to 4-mm diameter) of the parietal cortical surface (recording place) on the intact dura-mater. Tianeptine solutions with the following concentrations (mg/ml) were used: in the well-nourished rats, 0.5, 2, 5, 10 and 20; in the malnourished rats, 5, 10 and 20. Data are expressed as mean \pm S.E.M. **Control**: baseline CSD velocities, i.e., before tianeptine topical treatment. **Tianeptine**: maximal increase of CSD velocities obtained after tianeptine topical application. **Recovery**: CSD velocities after tianeptine cortical removal. The symbol # indicates that all malnourished values are significantly different from the corresponding well-nourished values ($P < 0.05$; ANOVA plus Tukey test). * $P < 0.05$ compared with the corresponding control period. \$ $P < 0.05$ compared with the other tianeptine concentrations. & $P < 0.05$ compared with the groups treated with 0.5 mg/ml and 2 mg/ml tianeptine solutions.

Since the serotonergic system starts to develop early in life (Azmitia and Whitaker-Azmitia, 1995; Lauder et al., 1981; Yew and Chan, 1999), we administered systemic tianeptine treatment to rats during the suckling period, and thus could analyze serotonergic influences during the brain growth spurt and their relationships with nutritional status.

Early tianeptine administration did not affect body weight, as there were no differences in body weight between treated animals and their respective controls injected with saline solution. Previous studies have shown a role for serotonin in promoting satiety (Blundell, 1992; Garattini, 1995; Silverstone, 1992; Simansky, 1996). Indeed, stimulation of the serotonergic system has been related with body weight reduction, and serotonergic drugs are currently used as adjuvant treatment to help reduce food ingestion (Redman and Ravussin, 2010). The main pharmacological mechanism of action of tianeptine is based on its capacity to reduce serotonin levels in several brain areas (Lechin et al., 2006; Mennini et al., 1987); accordingly, an increase in body weight could be expected following treatment. However, in contrast, hypophagia has been observed in rats after tianeptine treatment (Chaoulloff, 1993). Concerning nutritional status, our early-malnourished animals presented lower body weights compared to the well-nourished ones, and this weight difference persisted until adulthood when malnourishment was no longer present. This finding confirms previous data indicating that nutritional insult during development can have lasting effects on the body and/or brain (Rocha-de-Melo et al., 2006).

The main electrophysiological finding of this work was a tianeptine-induced increase in CSD propagation velocity. As mentioned above, this drug can reduce serotonin availability in the brain cortex (Mennini et al., 1987), which was the region in which we recorded CSD. We believe that the facilitating effect of tianeptine on CSD propagation probably depends on the pharmacological action of this drug on the serotonin system. The literature shows that CSD is antagonized by several drugs that enhance serotonergic activity, such as citalopram (Guedes et al., 2002), fluoxetine (Amancio-dos-Santos et al., 2006), d-fenfluramine (Cabral-Filho et al., 1995), and Sumatriptan (Read and Parsons, 2000). Furthermore, acute

administration of tryptophan (the precursor for serotonin synthesis) impairs CSD propagation (Trindade-Filho et al., 2009). These effects were attributed to the increase in brain cortical serotonin activity caused by such drugs. The present results reinforce previous data concerning a putative antagonistic influence of the serotonergic system on CSD propagation. They also clearly demonstrate that CSD velocity is modulated dichotomously, namely, with deceleration following synaptic serotonin increase (Amancio-dos-Santos et al., 2006) and acceleration following serotonin decrease (present results).

Serotonin seems to exert a mainly inhibitory role in the activity of the central nervous system (Cooper et al., 1996; Vogt, 1982). For instance, serotonergic system activation has been considered a useful strategy for treating diseases like epilepsy, migraine, and cerebral ischemia (Freitas et al., 2010; Lee et al., 2011; Monteith and Goadsby, 2011; Mostert et al., 2008; Trindade-Filho et al., 2008). The mechanisms underlying such diseases have been associated with changes in brain excitability, and seem to share some common features with those of CSD (Leão, 1944; Read and Parsons, 2000). The present findings additionally support this idea, and may contribute to the overall understanding of the relationship between CSD and these neurological diseases.

Oxidative stress has been implicated in the mechanism of cell death observed in seizures and cerebral ischemia (Betti et al., 2011), and antioxidants reduce this effect (Pestana et al., 2010). On the other hand, buspirone, a 5-HT_{1A} receptor agonist, reportedly exerts its anticonvulsant effects by inhibiting the development of oxidative stress (Freitas et al., 2010). Moreover, escitalopram, a selective serotonin reuptake inhibitor, seems to play the same protective role against ischemia-induced neuronal death (Lee et al., 2011). CSD has been considered as a sublethal stressor (Lian and Stringer, 2004), and it has been shown that antioxidants reduce the vulnerability of brain cells to oxidative stress associated with CSD, either directly or by upregulating genes involved in oxidative stress response (Choudhuri et al., 2002). These data suggest the involvement of oxidative stress in CSD, and raise the question of how the serotonin system may be related.

It is possible that serotonergic system stimulation could influence CSD by reducing its stressful action. Despite being an antidepressant, tianeptine decreases the serotonin availability in the brain, which may attenuate the physiological mechanisms that counteract the CSD-induced oxidative stress. This could explain the increase in CSD propagation velocities observed in the present work. In support of this hypothesis, tianeptine does not prevent oxidative stress in an experimental model for fragile X syndrome (Romero-Zerbo et al., 2009).

It is important to note that the effect of systemic tianeptine on CSD was influenced by the nutritional status; well-nourished, but not malnourished, animals treated with 10 mg/kg tianeptine presented increased CSD propagation velocities compared with the corresponding saline controls. Malnutrition reportedly modifies the action of some systemically injected substances on CSD (Guedes et al., 1992), with injections of glucose or diazepam modulating CSD velocity in well-nourished, but not in early-malnourished, animals (Costa-Cruz and Guedes, 2001; Guedes et al., 1992; Ximenes-da-Silva and Guedes, 1991). It has been suggested that malnutrition promoted hypo-responsiveness to those compounds. In another study, a reinforcement of the pilocarpine effect was observed in malnourished animals compared with the well-nourished controls (Vasconcelos et al., 2004). Taken together, the data collectively suggest that, depending on the involved neurotransmitter system, early malnutrition can increase or decrease CSD responses to certain compounds compared with the responses of the well-nourished brain. In the case of systemic tianeptine, malnutrition seems to diminish the drug

effect on CSD. Both the neurophysiological (serotonergic) and/or pharmacodynamic and pharmacokinetic mechanisms of tianeptine could have contributed to the current observations on malnutrition modulation. If this nutrition/CSD relationship can be demonstrated in humans, it could improve predictions of the effectiveness of distinct drugs therapeutically employed in the neurological clinic, as the effectiveness may change as a function of the early nutritional condition of the patient (Amancio-dos-Santos et al., 2006). Future experiments are required to test this assumption.

It is worth noting that topical application of tianeptine was more effective in accelerating CSD than systemic administration; however, systemic tianeptine administration is more important for use in humans than topical administration, since tianeptine is regularly administered systemically. In the well-nourished animals, we found that topical tianeptine significantly and dose-dependently facilitated CSD propagation. The difference between the systemic and topic CSD effects of tianeptine is not surprising, since topical application may not be influenced by the body's metabolism, as occurs for systemic treatment (Royer et al., 1988). It is well known that body metabolism can reduce drug activity (Royer et al., 1988). Similar systemic versus topical differences have been observed with other serotonergic drugs (Amancio-dos-Santos et al., 2006; Guedes et al., 2002). The study of topical application allows us to be more confident that the effects encountered here were possibly due to the modifications in brain serotonin availability, even though this amine concentration was not measured in the present study. Furthermore, the topical application experiments demonstrated that the CSD effects of tianeptine were fully reversible, as documented in Figs. 4 and 5.

In conclusion, our novel data indicate that tianeptine exerts a facilitating effect on CSD in the developing rat brain (as evidenced by the systemic experiments), as well as in the adult brain (topic application experiments). We also demonstrate that the effect of systemic tianeptine on the developing brain is modulated by nutritional status. Our results reinforce previous data that support an antagonistic role for the serotonergic system on CSD.

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